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Trapp, Stefan; Bomholtz, L.M.; Legind, Charlotte Nielsen

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Coupled Mother-Child Model for Bioaccumulation of POPs in Nursing Infants

Stefan Trapp[1,*], Li Ma[1] and Charlotte N. Legind[1,2]

1 Institute of Environment & Resources
Technical University of Denmark
Bygningstorvet 115
DK-2800 Kongens Lyngby
Denmark

2 Department of Agricultural Sciences
Faculty of Life Sciences
University of Copenhagen
Højbakkegård Allé 13
DK-2630 Taastrup
Denmark

* Corresponding author
Stefan Trapp
Institute of Environment & Resources
Technical University of Denmark
Bygningstorvet 115
DK-2800 Kongens Lyngby
Denmark

stt@er.dtu.dk
Tel +45 4525 1622
Fax +45 4593 2850

Capsule: This paper addresses a model for accumulation of organic compounds by mother and breast-fed infant, applicable for exposure assessment within larger frameworks.

Abstract

Bioaccumulation of persistent organic pollutants (POPs) leads to high levels in human milk and high doses of POPs for nursing infants. This is currently not considered in chemical risk assessment. A coupled model for bioaccumulation of organic chemicals in breastfeeding mother and nursing infant was developed and tested for a series of organic compounds. The bioaccumulation factors (BAF) in mother, breast milk and child were predicted to vary with log Kow and, for volatile compounds, with Kaw and concentration in air. The concentrations of POPs in the infant body increase the first half year to about factor 3 above mother and decline thereafter to lower levels. The predicted results are close to empirical data and to an empirical regression. The new mother-child model is compact due to its easy structure and the analytical matrix solution. It could be added to existing exposure and risk assessment systems, such as EUSES.

Keywords: Accumulation; Breast milk; Human exposure; Infant; Model; POP

1 Introduction

Persistent organic pollutants (POPs) are "chemicals that remain intact in the environment for long periods, become widely distributed geographically, accumulate in the fatty tissue of living organisms, and are toxic to humans and wildlife" (UNEP 2007). POPs, such as polychlorinated dibenzodioxins and -furans (PCDD/F), polychlorinated biphenyls (PCB) and chloroorganic pesticides, have been detected in human milk samples all over the world (Rogan et al. 1986, Schecter et al. 1996, Filser et al. 1997, Raab et al. 2007, Shen et al. 2007, Wittsiepe et al. 2007, Tanabe and Kunisue 2007). This raised considerable concern about adverse health effects on nursing infants (Harrison 2001, CEHAPE 2004, US EPA 2006).

The uptake of POPs, such as PCDD/F, by adults is mainly via food ingestion (Travis and Hattemeyer-Frey 1991). The uptake by nursing infants via breast milk has been reported to be higher than by adults via diet, for some POPs at levels above the acceptable daily intake (Dahl et al. 1995, Kreuzer et al. 1997, Schade and Heinzow 1998, BGVV 2000, Tanabe and Kunisue 2007). POPs may accumulate for a longer period in the body of the mother and then be transferred to the nursing infant via mother's milk. Travis et al. (1988) developed empirical relations for the accumulation of chemicals in human adipose tissue and human milk. The regressions are based on 12 (tissue) or 6 (milk) organic chemicals with a log K_{OW} between 1.32 and 6.50 (tissue) or 5.16 to 6.50 (milk). The bioaccumulation factors B_f (tissue) and B_m (milk) were defined as

$$B_f = \frac{\text{Concentration of organic in adipose tissue (mg/kg lipid)}}{\text{Average daily intake of organic (mg/d)}}$$

$$B_m = \frac{\text{Concentration of organic in breast milk (mg/kg lipid)}}{\text{Average daily intake of organic (mg/d)}}$$

Travis et al. (1988) related these bioaccumulation factors to the log K_{OW} of the substances.

$$B_f = 2.0 \times 10^{-4}\ Kow^{1.05} \quad \left[\frac{d}{kg}\right] \quad (n=12, r=0.98)$$

$$B_m = 9.8 \times 10^{-5}\ Kow^{1.14} \quad \left[\frac{d}{kg}\right] \quad (n=6, r=0.97)$$

Besides this empirical approach, several mathematical model approaches exist to predict human tissue concentrations after uptake, e.g. the models prepared by Kreuzer et al. (1997) or Filser et al. (1997) and Maruyama et al. (2003) for PCDD/F. Accumulation in the food chain with subsequent accumulation in humans was addressed by Czub and McLachlan (2004a,b). To summarize, compound-specific models, comprehensive numerical models and also easy empirical models for the prediction of the accumulation of POPs in humans are available.

However, what lacks is a model predicting accumulation of POPs or other compounds in breastfeeding mother and nursing infant after uptake of chemicals via diet or other relevant sources by mother, which is compact enough to be combined with other models

and estimation routines, e.g., for chemical safety assessment tools such as EUSES (EC 1996).

"Traditional risk assessment approaches and environmental health policies have focused mainly on adults and adult exposure patterns, utilizing data from adult humans or adult animals" (CEHAPE 2004). Indeed, current chemical risk assessment in the EU (EC 2003) considers only grown-ups (70 kg bodyweight). An additional focus on children and in particular nursing infants, which are one trophic level higher and are eventually also more sensitive to chemicals, requires a compact exposure estimation method that can run with a minimum data set.

This paper addresses the development, parameterization, sensitivity analysis, validation and application of a coupled model for accumulation of organic compounds by nursing mother and child. The coupled differential equations were solved analytically. The model was tested with 2,3,7,8-TCDD and compared to empirical data for 11 other compounds collected by Travis et al. (1988).

2 Methods

2.1 Model Development

Figure 1 gives an overview of the system considered by the model. The human body is considered as a flux-through system. The input of chemical occurs via diet (mother) or milk (child) and inhalation (both). Inside the body, phase equilibrium is assumed. The compound is eliminated from the body by exhalation and excretion (both together are named "outflux"), by metabolism and, in case of the nursing mother, with breast milk.

<Figure 1>

Mother before birth of the child

The input of chemical into the mother is independent of the concentration in her body, C_H, while the output is proportionally related to it. This yields a linear differential equation for the mass balance of the form

$$\frac{dm}{dt} = I - k \times m \qquad (1)$$

where m [mg] is the mass of chemical in the human body, I [mg d^{-1}] is the sum of daily uptake of chemical and k [d^{-1}] is the loss rate constant.

The input I can be derived from measurements or exposure assessments. The loss rate constant k is calculated from the flux of chemical out of the body.

147

148 The human body is considered as composed of the phases lipids and water. Lipids were
149 assumed to dissolve the chemical similar to octanol. The phase equilibrium between
150 concentration in human body, C_H [mg kg^{-1}], and concentration in water, C_W [mg L^{-1}], is

151

152 $$K_{HW} = \frac{C_H}{C_W} = W_H + \frac{L_H}{\rho_L} \times K_{OW} \qquad \left[\frac{L}{kg}\right] \qquad (2)$$

153

154 where K_{HW} is the partition coefficient human body to water [L kg^{-1}], W_H is the water
155 content [L kg^{-1}] and L_H is the lipid content of the human body [kg kg^{-1}], ρ_L is the density
156 of lipids [kg L^{-1}] and K_{OW} [L L^{-1}] is the partition coefficient between octanol and water.

157

158 The change of chemical mass in time due to outflux of chemical from the body dm_F/dt
159 [mg d^{-1}] is the sum of outflux with water, lipid and air

160

161 $$\frac{dm_F}{dt} = F_W \times C_{F,W} + F_L \times C_{F,L} + F_A \times C_{F,A} = F \times C_F \qquad \left[\frac{mg}{d}\right] \qquad (3)$$

162

163 where F_W is the outflux of water [L d^{-1}], F_L is the outflux of lipids [kg d^{-1}] (with feces)
164 and F_A is the outflux of air [L d^{-1}] (exhalation). $C_{F,W}$ [mg L^{-1}], $C_{F,L}$ [mg kg^{-1}] and $C_{F,A}$ [mg
165 L^{-1}] are the concentrations in the water, lipid and gas fraction of the outflux; C_F [mg kg^{-1}]
166 is the weighted average concentration in the outflux. The total material outflux F [kg d^{-1}]
167 is the sum of the outfluxes of water, lipids and air,

168

169 $$F = F_W \times \rho_W + F_L + F_A \times \rho_A \qquad \left[\frac{kg}{d}\right] \tag{4}$$

170

171 Using the assumption of phase equilibrium we can rewrite to

172

173 $$F \times C_F = F \times f_W \times C_{F,W} + F \times f_L \times K_{OW} \times C_{F,W} + F \times f_A \times K_{AW} \times C_{F,W} \tag{5}$$

174

175 where K_{AW} is the partition coefficient [L L^{-1}] between air and water (also known as
176 dimensionless Henry's Law constant), and f are the flux fractions [L/d : kg/d] of water W,
177 lipids L and air A of the total flux F,

178

179 $$f_W = \frac{F_W}{F},\ f_L = \frac{F_L/\rho_L}{F} \text{ and } f_A = \frac{F_A}{F} \qquad \left[\frac{L}{kg}\right] \tag{6}$$

180

181 The average concentration of chemical in the outflux, C_F, is then

182

183 $$C_F = f_W \times C_{F,W} + f_L \times K_{OW} \times C_{F,W} + f_A \times K_{AW} \times C_{F,W} \tag{7}$$

184

185 Note that for phase equilibrium, $C_{F,W}$ (concentration in aqueous phase of outflux) equals
186 C_W (concentration in aqueous phase of human body), and thus we derive

187

188 $$K_{FW} = \frac{C_F}{C_W} = f_W + f_L \times K_{OW} + f_A \times K_{AW} \qquad \left[\frac{L}{kg}\right] \tag{8}$$

189

where K_{FW} [L kg^{-1}] is the partition coefficient between outflux [kg d^{-1}] and water [L d^{-1}]. Then, the partition coefficient between human body and outflux, K_{HF} [kg/kg], is

$$K_{HF} = \frac{C_H}{C_F} = \frac{K_{HW}}{K_{FW}} \qquad \left[\frac{kg}{kg}\right] \tag{9}$$

where C_H and C_F are the concentrations [mg kg^{-1}] in human body and outflux in phase equilibrium. It follows for the loss rate constant k [d^{-1}] in eq. 1, which is the sum of the losses by outflux and by metabolism or degradation with first-order k_{deg} [d^{-1}]

$$k = \frac{F}{M_H \times K_{HF}} + k_{\text{deg}} \qquad \left[\frac{1}{d}\right] \tag{10}$$

where M_H [kg] is the bodyweight. The analytical solution of equation (1) for the chemical mass m [mg] in human body at time t is

$$m(t) = m_0 \times e^{-kt} + \frac{I}{k}(1 - e^{-kt}) \tag{11}$$

which gives in steady-state ($t \rightarrow \infty$)

$$m(\infty) = \frac{I}{k} \tag{12}$$

Concentrations C_H [mg/kg] in the human body were derived from $C_H=m/M_H$, assuming a constant bodyweight M_H

$$C_H(\infty) = \frac{m(\infty)}{M_H} = \frac{I}{k \times M_H} \qquad \left[\frac{mg}{kg}\right] \qquad (13)$$

This solution was used to calculate the concentration of chemical in the woman before birth of the child (and before pregnancy, the bodyweight is constant at 60 kg).

Nursing mother with child

In this scenario, the mother gives birth to a child and nurses the infant. Equations for the mother were modified, and new equations for breast milk and nursing child were introduced.

Mother. Nursing changes the outflux from the mother. Milk consists in the model of water and lipids. The flux of milk F_M [kg d^{-1}] was added to the outflux F in equation (4)

$$F = F_W \times \rho_W + F_L + F_A \times \rho_A + W_M \times \rho_W \times F_M + L_M \times F_M \qquad \left[\frac{kg}{d}\right] \qquad (14)$$

where W_M [L kg^{-1}] is the water content and L_M [kg kg^{-1}] is the lipid content of human milk. Fractions of outflux [L kg^{-1}] f_W, f_L and f_A were recalculated for the case of nursing.

231 $$f_W = \frac{F_W + W_M \times F_M}{F},\ f_L = \frac{F_L + L_M \times F_M}{F \times \rho_L} \text{ and } f_A = \frac{F_A}{F} \qquad \left[\frac{L}{kg}\right] \qquad (15)$$

232

233 The other equations (eqs. 1,2, 8-13) were applied without changes, but the new values of

234 F and f were entered.

235

236 **Milk.** With breast milk, chemical is lost from the mother and transferred to the baby

237 (Schecter et al. 1996). To calculate the concentration of chemical in milk, phase

238 equilibrium between milk and mother was assumed. The concentration in milk C_M [mg

239 kg^{-1}] is

240

241 $$C_M = K_{MH} \times C_H \qquad \left[\frac{mg}{kg}\right] \qquad (16)$$

242

243 where K_{MH} [kg kg^{-1}] is the partition coefficient between milk and human. The partition

244 coefficient milk to water K_{MW} [L kg^{-1}] is

245

246 $$K_{MW} = \frac{C_M}{C_W} = W_M + \frac{L_M}{\rho_L} \times K_{OW} \qquad \left[\frac{L}{kg}\right] \qquad (17)$$

247

248 The partition coefficient between milk and human body K_{MH} [kg/kg] is then

249

250 $$K_{MH} = \frac{C_M}{C_H} = \frac{K_{MW}}{K_{HW}} \qquad \left[\frac{kg}{kg}\right] \qquad (18)$$

Child. The breast-fed infant can take up chemicals by breast milk and by inhalation. Breathing is external input to the child, $I_C = F_A \times C_A$, where F_A [here: $m^3\ d^{-1}$] is the flux of inhaled air and C_A [$mg\ m^{-3}$] is the concentration of chemical in air. Loss of chemical occurs via outflux and by metabolic elimination with first-order rate constant k_{deg} [d^{-1}]. The mass balance for the child is

$$\frac{dm_C}{dt} = I_C + C_M \times F_M - C_F \times F_C - k_{\deg} \times m_C \qquad (19)$$

where C_M [$mg\ kg^{-1}$] denotes the concentration in breast milk, F_M [$kg\ d^{-1}$] is the flux of milk from mother to child, C_F [$mg\ kg^{-1}$] is the concentration in the outflux of the child and F_C [$kg\ d^{-1}$] is the outflux from the child.

Using the partition coefficients, the equation can be rewritten to

$$\frac{dm_C}{dt} = I_C + K_{MH}\frac{F_M}{M_H} \times m_H - \frac{F_C}{K_{CF} \times M_C} \times m_C - k_{\deg} \times m_C \qquad \left[\frac{mg}{d}\right] \qquad (20)$$

where m_H [mg] is the chemical mass in mother (human H), m_C [mg] is the chemical mass in the child, K_{CF} [$kg\ kg^{-1}$] is the partition coefficient between child and outflux and M_C [kg] is the body mass of the child. The phase equilibrium between child body (index C) and water (index W) is

273 $$K_{CW} = \frac{C_C}{C_W} = W_C + \frac{L_C}{\rho_L} \times K_{OW} \qquad \left[\frac{L}{kg}\right] \qquad (21)$$

274

275 where K_{CW} [L kg^{-1}] is the partition coefficient child body to water, C is the equilibrium
276 concentration in child, index C [mg kg^{-1}], or water, index W [mg L^{-1}], W_C [L kg^{-1}] is the
277 water content and L_C [kg kg^{-1}] is the lipid content of the child body. The initial
278 concentration in the child $C_C(0)$ [mg kg^{-1}] was calculated from phase equilibrium to
279 mother

280

281 $$C_C(0) = \frac{K_{CW}}{K_{HW}} \times C_H \qquad (22)$$

282

283 The outflux F_C [kg d^{-1}] from the child was summed up, as was done for the outflux from
284 the mother:

285

286 $$F_C = F_W \times \rho_W + F_L + F_A \times \rho_A \qquad (23)$$

287

288 where indeces W, L and A indicate water, lipid and air. Again, the flux fractions were
289 used to calculate the phase equilibrium between outflux and water, K_{FW}:

290

291 $$K_{FW} = \frac{C_F}{C_W} = f_W + f_L \times K_{OW} + f_A \times K_{AW} \qquad \left[\frac{L}{kg}\right] \qquad (24)$$

292

293 The partition coefficient between child body and outflux, K_{CF} [kg/kg], is

$$K_{CF} = \frac{C_C}{C_F} = \frac{K_{CW}}{K_{FW}} \qquad \left[\frac{kg}{kg}\right] \tag{25}$$

2.2 Matrix Solution

The differential equations of mother and child are coupled and were treated as a linear 2×2 matrix system of the form

$$\frac{dm_1}{dt} = a_{11}m_1 + a_{12}m_2 + I_1 \tag{26}$$

$$\frac{dm_2}{dt} = a_{21}m_1 + a_{22}m_2 + I_2 \tag{27}$$

Matrix element 1 is the mother. The matrix constant a_{11} [d^{-1}] is the sum of all loss processes from the mother and is identical with the negative loss rate k (eq. 10). The matrix constant a_{12} [d^{-1}] is what mother receives from the child and is zero (therefore, the equation for chemical mass in mother can be solved independently of that for the child, eqs. 1 and 11). Input I_1 [mg d^{-1}] is the sum of all input to mother.

Matrix element 2 is the nursed child. The matrix constant a_{21} [d^{-1}] describes the transfer via milk from mother to child, $a_{21}=K_{MH}\times F_M/M_H$. The matrix constant a_{22} [d^{-1}] describes all losses of chemical from the child, $a_{22} = -F_C/(K_{CF}\times M_C) - k_{deg}$. Input I_2 includes all chemical input independent from the mother, i.e. via inhalation, $I_2=F_A\times C_A$. A standard solution for this system of differential equations exists for the case of constant rates and

315 inputs (Nazaroff and Alvarez-Cohen 2001). Concentrations [mg/kg] were derived by
316 dividing the chemical mass [mg] by the bodyweight [kg].
317
318 **2.3 Parameterization of the Model**
319 Input data (Table 1) was selected from several sources, preferably from existing models
320 (Kreuzer et al. 1997, Czub and McLachlan 2004b), in order to allow a comparison of the
321 results. The application of the steady-state solution (eqs. 12, 13) for the mother before the
322 birth of her child avoids the need to chose an appropriate initial mass m_0 for the first
323 generation. The 95%-steady-state is reached for latest t=18 years for all chemicals with
324 the default parameterization.
325
326 The total daily uptake I [mg d^{-1}] was calculated as the sum of uptake via diet i_D [mg/d]
327 and inhalation of air:
328
329 $$I = i_D + F_A \times C_A \qquad \left[\frac{mg}{d}\right] \tag{28}$$
330
331 For the breast-fed baby, i_D is 0.
332
333 Outflux of lipids was assumed to be 10% of lipids in the diet. With 70 g d^{-1} as average
334 lipid ingestion, 0.007 kg d^{-1} outflux of lipids results. For the baby, 0.0045 kg d^{-1} (1/10 of
335 influx of lipids with milk) was used. Table 1 lists the input data chosen as default for the
336 model and used in the following simulations.
337

338 To calculate concentrations in the body of the child during the simulation period, the
339 respective bodyweight was used, to account for growth effects. The bodyweight of the
340 child with age (in years) was approximated by a second-order polynom fitted to growth
341 data for girls in Germany (Hesse et al. 1997) (eq. 29)
342
343 $$bw = -0.053 \times age^2 + 3.76 \times age + 3.54 \qquad (n=36,\ R^2=0.98) \qquad (29)$$
344
345 **<Table 1>**
346

3 Results

3.1 Example Simulation TCDD

To illustrate the general behaviour of the model, an example simulation with 2,3,7,8-tetrachlordibenzo-*p*-dioxin (TCDD) was performed. TCDD is a highly toxic, persistent lipophilic (log K_{OW} 6.76) and semivolatile (K_{AW} 0.0015) compound (Rippen 1991). The concentration of TCDD in air was set to 4 fg m^{-3} (background concentration in Southern Germany, McLachlan 1992). Ingestion of TCDD by the mother with diet was 25 pg d^{-1} (Kreuzer et al. 1997). Figure 2 shows the simulated concentration of TCDD in lipids for mother and child over a three-years period. The starting concentration of the mother [3.6 ng kg^{-1} lipid] is the steady-state concentration (eq. 13). For t>0, the matrix solution was applied. For t>0, the concentration of TCDD in mother decreases exponentially and falls to 63% of the initial concentration after 1/2 year and to 42% after 1 year of nursing. The initial concentration in the infant [3.6 ng kg^{-1} lipid] is in equilibrium to mother. It steeply increases to 12.3 ng kg^{-1} lipids after ½ year. Hereafter, it falls, due to depletion of the mother's body burden and growth dilution, to 8.8 ng kg^{-1} lipids after 1 year and to 1.73 ng kg^{-1} lipid after 3 years (of course, 3 years nursing is rare). The concentration in lipids of milk is identical to that in lipids of the mother body and was not plotted. During the period of nursing, the loss of TCDD from mother with milk is higher than the daily intake, which is the reason for the depletion of TCDD from the body of the mother. Figure 3 shows the ratio of the TCDD-dose taken up by the infant (per kg bw) divided by the dose taken up by the mother (25 pg d^{-1} =0.42 pg kg^{-1} bw d^{-1}). The ratio is initially 110 and falls later to 45 (t=1/2a), 22 (t=1a) and 4.5 (t=3a). The dose ratio is much higher than

370 the concentration ratio (Figure 2). Uptake of TCDD with air is neither for mother
371 (inhalation 11 m3 per day, uptake 44 fg TCDD per day) nor infant (inhalation 4.5 m3 per
372 day, uptake 18 fg TCDD per day) of relevance. The maximum concentration ratio child
373 to mother is reached after t=1/2a. The concentration in the child is maximally 3.4times
374 that in mother before birth and falls to 2.5times (t=1a) and to 0.48times (t=3a), due to
375 rapid elimination and growth dilution. The calculated elimination half-time (ln 2 divide
376 by rate constant k) of TCDD from the body is 4.6 years for the mother before birth, 0.6
377 years for the nursing mother and only 0.34 years for the infant.
378 These simulation results can be confronted to empirical data (Kreuzer et al. 1997, Filser
379 et al. 1997). Measured concentrations of TCDD in lipids of adipose tissue and blood for
380 adults in Germany early 1990ies range from <0.1 ng kg^{-1} lipid to 16 ng kg^{-1} lipids, with
381 an average background level of 3 ng kg^{-1} lipids (Filser et al. 1997). Concentrations in
382 breast milk vary between 1 and 3.9 ng kg^{-1} lipids, decreasing during the period of
383 nursing, with an average of about 2 ng kg^{-1} lipids. TCDD-concentrations in stillborn
384 range from of 1.3-2.1 ng/kg lipids. Concentrations of TCDD in lipids of adipose tissue,
385 faeces and blood of infants did not differ much and ranged from <0.2 to 7.3 ng kg^{-1} lipids.
386 TCDD levels in adipose tissue of 20 breast-fed infants aged between 0 and 44 weeks
387 ranged from 0.16 to 4.1 ng kg^{-1} tissue and were higher than that of non-breast-fed
388 children (0.16-0.76 ng kg^{-1} lipids) (Kreuzer et al. 1997). Predicted half-life of TCDD in
389 infants was short (0.42 years), and increased to about 10 years for adults between 40 and
390 60 years of age. These results are throughout close to the outcome of the simulations with
391 the mother-child model, without any conflicting results.
392 **<Figure 2> <Figure 3>**

4 Discussion

4.1 Comparison of Regression and Mother-Child Model

The regression of Travis et al. (1988) uses only one physico-chemical parameter, the K_{OW}, while the mother-child model requires K_{OW} and K_{AW}. The bioaccumulation factors (BAF), related to concentration in lipids, derived from model and regression were compared. The concentration in air was set to 0. The steady-state BAF of mother at birth of the child (t=0) and the BAF milk after t=½ year were plotted in Figure 4. The BAF for mother and milk are practically identical, except for very hydrophilic compounds (the relation to lipids gives artificially higher concentrations for milk if compounds do not partition into lipids). The model BAF differ more than two orders of amount with low (10^{-9}) or high (0.1) K_{AW} except for high log K_{OW}, because volatile compounds are rapidly lost from the body via exhalation. Within its regression range (log K_{OW} 1.32 to 6.50), the regression gives similar results as the model with high K_{AW}, probably because the less lipophilic compounds in the training set of the regression were all solvents with high K_{AW} (Table 2). With increasing lipophilicity, the BAF predicted by the mother-child model reach a plateau (mother at t=0: BAF is 143 [d kg^{-1} lipid], milk at t=0.5 years: BAF is 90 [d kg^{-1} lipid]), while the BAF derived by the regression increase unlimited with K_{OW}. This is unrealistic, except for short time-periods, as the loss of super-lipophilic compounds via milk would be several orders of amount higher than the daily intake. The daily intake (1 mg d^{-1}) is balanced at a BAF milk (4.5% lipids) of 22 [d kg^{-1} lipid]. The regression gives a BAF=22 [d kg^{-1} lipid] with log K_{OW} =4.7, but higher BAF for all log K_{OW} above that value. Contrary, the steady-state (t=∞) BAF milk predicted by the mother-child model for

416 compounds with log K_{OW} > 4.7 is constant at 19 [d kg^{-1} lipid]. In the initial period of
417 nursing, the BAF milk is above steady-state, therefore, mother is depleted from POPs by
418 nursing (Fig. 2).
419
420 **<Figure 4>**
421
422 **4.2 Uptake via inhalation compared to uptake via food**
423
424 The impact of exhalation on BAF of hydrophilic to medium lipophilic compounds (log
425 K_{OW} < 5) is evident from Figure 4: fugitive compounds with high K_{AW} show much lower
426 bioaccumulation, due to this process. On the other hand, the K_{AW} may also impact the
427 uptake by inhalation. Basically, this uptake is calculated from the product of
428 concentration in air and inhalation (eq. 28). Under certain conditions, such as ubiquitous
429 background distribution of persistent compounds, we may assume that the concentrations
430 in diet and air are near phase equilibrium. Using the formalism of section 2.1, the
431 equilibrium ratio K_{DA} [m^3 kg^{-1}] between concentration in diet C_D [mg kg^{-1}] and in air C_A
432 [mg L^{-1}] is
433

434 $$\frac{C_D}{C_A} = K_{DA} = \frac{W_D + L_D \times K_{OW}}{K_{AW}} \qquad \left[\frac{L}{kg}\right] \qquad (30)$$

435
436 where W_D is the water content [kg kg^{-1}] and L_D is the lipid content [kg kg^{-1}] of the diet.
437
438 The relation between the input data i_D (uptake of chemical with diet, mg d^{-1}) and C_D is

$$i_D = C_D \times F_D \quad (31)$$

where F_D is the daily dietary consumption [kg d^{-1}]. Thus, the equilibrium concentration in air $C_{A,eq}$ [mg L^{-1}] is

$$C_{A,eq} = \frac{i_D}{K_{DA} \times F_D} \quad (32)$$

The dose via inhalation i_A [mg d^{-1}] is subsequently

$$i_A = F_A \times C_{A,eq} \quad (33)$$

where F_A is the inhalation of air [mother 11 m^3 d^{-1} and child 4.5 m^3 d^{-1}].

A typical diet of an adult Danish female (F_D) contains 60 g lipids and 2 L water, hereof 1.4 L drinking water. Using these numbers, the ratio of uptake via air to uptake via diet, assuming phase equilibrium between air and food (including water), was calculated.

Figure 5 shows that the relevance of inhalation as uptake pathway for chemicals into the human body depends much on the value of the partition coefficient air to water K_{AW}. For non-volatile compounds (low K_{AW}, 10^{-6} L L^{-1}), inhalation is not relevant at all. With very low K_{AW} (10^{-9} L L^{-1}), the ratio of uptake with inhalation versus uptake with diet is never

461 above 1 : 100 000 (not shown). On the other hand, inhalation is the dominant way of
462 entry into the body for volatile compounds (high K_{AW}, 0.1 L L^{-1}) with up to log K_{OW} 4.
463 With moderate K_{AW} (10^{-3} L L^{-1} in Fig. 5), the relative importance of inhalation for the
464 body burden decreases, but it is still higher than uptake by diet for the less lipophilic
465 compounds (log $K_{OW} \leq 2$). For lipophilic compounds (log $K_{OW} > 5$), which have the
466 highest bioaccumulation, uptake by inhalation is generally not of much relevance.
467 Compared to the mother, uptake via inhalation has similar (hydrophilic compounds) or
468 lower importance (lipophilic compounds) for the child.
469
470 Note that these calculations were done for the rare case of near-equilibrium conditions. In
471 real life, many individuals live in urban centers, while the agricultural production is in
472 remote rural areas. It may be expected that the air pollution is higher in the cities, in
473 particular when additional indoor sources of pollutants are present. Furthermore,
474 lipophilic compounds may be strongly adsorbed to particles, which are inhaled
475 simultaneously with air. Thus, these conclusions are surely not of general validity, and
476 the relative importance of inhalation for the uptake of pollutants may be higher in real life
477 than expected from the calculations displayed in Fig. 5.
478
479 **<Figure 5>**
480
481 **4.3 Validation Against Empirical Data**
482 To derive their regressions for bioaccumulation in adipose tissue and breast milk, Travis
483 et al. (1988) collected twelve bioaccumulation factors (BAF) for human adipose tissue

484 and six BAF for breast milk from literature and pharmacokinetic models. The model was
485 tested against these data. Additionally, BAF for TCDD were calculated from data in
486 Kreuzer et al. (1997). The concentrations are related to lipid content. Log K_{OW}-values
487 given in the original reference (Travis et al. 1988) were used, except for TCDD (Rippen
488 1991) (Table 2). One compound, pentachlorophenol, had to be excluded from the analysis
489 because it is not a neutral compound but a weak acid (Rippen 1990). The uptake of weak
490 electrolytes into living cells follows principles which are not covered by the model
491 (Trapp 2004).
492
493 **<Table 2>**
494
495 In order to reproduce the experimental conditions under which empirical BAF were
496 derived, concentration in air was set to zero. Figure 6 shows the measured BAF for
497 human adipose tissue of the 12 organic compounds, the results from the regression by
498 Travis et al. (1988) and the model outcome for mother before birth at steady-state. The
499 measured BAF range from 0.013 (TCE) to 724 (DDE) and are lowest for the volatile
500 compounds with low log K_{OW}. Naturally, the regression predicts this range, and its results
501 are generally less than factor 5 from the measurements, except for TCDD (over-predicted
502 factor 21), which is out of the regression range. The model simulations, too, are close to
503 the measured data. The results differ maximally factor 7 (dieldrin). The averaged ratio
504 between predicted and measured BAF is 1.54 for the regression (3.15, including TCDD)
505 and 2.0 for the model (including TCDD).
506

Figure 7 shows the measured BAF for human milk of seven organic compounds. The measured BAF range from 43 (dieldrin) to 1660 (PCB). The regression results are quite close to the measured BAF, except for TCDD. To derive the BAF, averaged values from milk samples in the period between birth and up to 18 month after birth have been used (Rogan et al. 1986). Therefore, the measured BAF were compared to the model result at birth (t=0) and for t=1 year. The calculated BAF milk are higher for t=0 and do not vary much, as all compounds are lipophilic with log K_{OW}>4.7. The predicted BAF are somewhat too low, except for dieldrin and TCDD. The largest deviation is seen for PCB, which is not a single compound but a mix of 209 congeners. The averaged ratio between regression result and measured BAF is 2.02 (1.09 without TCDD). The ratio between model prediction and measurements is 0.99 (0.87 without TCDD) for t=0 and 0.42 (0.37 without TCDD) for t=1 year.

<Figure 6> <Figure 7>

4.4 Comment on Nursing

The question is often raised whether nursing may have an adverse impact on the health of the child (BgVV 2000). While the high dose of POPs (here: TCDD) that the infant receives with breast milk suggests so, the moderate increase of infant body concentration gives less reasons to be concerned. There is evidence that after a few life-years, the difference between breast-fed and formula-fed infants in their body-burden with POPs, such as TCDD, vanishes (Kreuzer et al. 1997). If the mother nurses more than one child without longer periods in between, the model predicts lower body-burdens for the later

530 children, i.e., for the second child after one year nursing, the body concentration is about
531 the same as in the mother, if she never had breast-fed. Empirical studies confirm that the
532 first born child is at higher risk to be exposed to POPs that have accumulated in mother
533 and are transferred via mother milk (Tanabe and Kunisue 2007), and that levels of POPs
534 decrease during lactation (Harris et al. 2001). An argument pro nursing may also be that
535 the mother reduces her POP pool (Schecter et al. 1996). Metabolism in the body of the
536 mother reduces the dose transferred to the nursing infant. With metabolism half-times
537 below 14 days, the model predicts that the dose the nursing infant receives is always
538 below the dose for the mother. According to the model, the mother has a "filter effect" for
539 less lipophilic and volatile compounds: for those, the dose for the infant via breast milk is
540 lower than the dose mother takes up (per kg bodyweight) (Figure 4).
541

542 **4.5 Limitations and Application Range of the New Model**

543 The new mother-child model is, due to the underlying equations for phase equilibrium,
544 not valid for inorganic (Wuenschmann et al. 2008) and electrolytic organic compounds
545 (Trapp 2004, Trapp and Horobin 2005). The assumption of phase equilibrium within the
546 body for neutral lipophilic organic compounds is supported by the results of Kreuzer et
547 al. (1997), who found comparable levels of TCDD in lipids of adipose tissue, feces,
548 blood, liver, breast milk and new-borns. Deviations from equilibrium could in particular
549 occur for compounds with rapid metabolism. However, for those the model predicts low
550 transfer into infants anyhow, thus, a "false alarm" due to over-prediction would not occur,
551 if accurate metabolism rate constants are at hand.
552

553 The new mother-child model is more complex than the regression of Travis et al. (1988),
554 but still the structure is relatively easy, and the analytical solution of the differential
555 equations keeps the calculations compact and robust. The model requires five chemical
556 input parameters (i_D, K_{OW}, C_A, K_{AW} and k_{deg}). It may be more troublesome to acquire these
557 data, but the differences in the accumulation behavior of persistent and reactive
558 compounds can be considered, and uptake via diet and inhalation can be calculated
559 simultaneously or separately. Therefore, results from diet studies can be used as input
560 data, and bioaccumulation factors as defined by Travis et al. (1988) can be calculated,
561 using i_D =1 mg d^{-1} and C_A =0. The regression necessarily will fail if uptake from air plays
562 a major role.
563
564 Another advantage of the deterministic approach, compared to empirical relations, is that
565 the relevant processes behind the BAF can be identified. The variation of physiological
566 parameters (for the human body) allows to determine the influence of age, diet,
567 bodyweight, growth, metabolism etc. Furthermore, the regression violates the mass
568 balance for more lipophilic compounds with high log K_{OW} and gives unrealistically high
569 BAF, as was shown before.
570
571 In comparison to more sophisticated models for bioaccumulation (Kreuzer et al. 1997,
572 Molen et al. 1996, Maruyama et al. 2003), the new mother-child model is more compact
573 and more variable (i.e., it does not require the measurement of any chemical-specific
574 data, besides the minimum data set, and it needs no calibration steps). Compared to the
575 human bioaccumulation model ACC (Czub and McLachlan 2004b), which calculates the

576 body concentration of a single human over the whole life-time, the mother-child model is
577 less complex and more flexible, due to the analytical solution. If, for the purpose of risk
578 assessment, only the dose for the infant is required, the differential equation system is
579 decoupled, and the solution for the breast-feeding mother alone can be solved (eq. 11).
580
581 The development of the new mother-child model was driven by the need to predict the
582 exposure of nursing children within the framework of chemical risk assessment and/or
583 risk assessment of polluted sites. Model systems for these purposes exist (EC 1996,
584 Rikken et al. 2001, Kulhanek et al. 2004) but none of them considers nursing infants (in
585 fact, children are not considered at all in most of them). The new model could be added
586 with small effort to existing exposure assessment tools, in order to fill this gap.
587

588 **Model availability**

589 The new mother-child model is available as unprotected excel-spreadsheet version from
590 the first author. Please mail to stt@er.dtu.dk.
591

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741 **Table 1.** Default input data for the mother-child model.

Parameter	Symbol	Value	Unit	Reference
Mother				
Age	t	25	a	Kreuzer et al. (1997)
Body mass	M_H	60	kg	Maruyama et al. (2003)
Body water fraction	W	0.71	L/kg	Czub and McLachlan (2004b)
Body lipid fraction	L	0.284	kg/kg	Deurenberg et al. (1991)
Outflux of water	F_W	1.24	L d^{-1}	Maruyama et al. (2003)
Outflux of lipid	F_L	0.007	kg d^{-1}	10% of lipids in diet
In/exhalation of air	F_A	11	m^3 d^{-1}	Layton (1993)
Breast milk data				
Milk flux	F_M	1	kg d^{-1}	Kreuzer et al. (1997)
Milk water content	W_M	0.87	L kg^{-1}	Czub and McLachlan (2004b)
Milk lipid content	L_M	0.045	kg kg^{-1}	Kreuzer et al. (1997)
Child				
Age	t	0 - 3	a	
Body mass	M_b	3.5 - 7.25	kg	Hesse et al. (1997)
Body water fraction	W	0.71	L/kg	Czub and McLachlan (2004b)
Body lipid fraction	L	0.233	kg/kg	Deurenberg et al. (1991)
Outflux of water	F_W	0.87	L d^{-1}	water content of 1 kg milk
Outflux of lipid	F_L	0.0045	kg d^{-1}	10% of influx
Outflux of air	F_A	4.5	m^3 d^{-1}	Layton (1993)
Other data				
Density of water	ρ_W	1	kg L^{-1}	
Density of lipids	ρ_L	0.82	kg L^{-1}	
Density of air	ρ_A	1.3×10^{-3}	kg L^{-1}	

742

743 **Table 2.** Names and physico-chemical data of the compounds in Travis et al. (1988).

Abbreviation	Compound	log K_{OW} [a]	K_{AW} [b]
Benzene	benzene	2.13	0.23
DDE	1,1-bis(4-chlorphenyl)-2,2-dichlorethen	5.83	0.05
DDT	1,1-bis(4-chlorphenyl)-2,2,2-trichlorethan	5.76	0.0016
DCM	dichlormethane	1.32	0.087
Dieldrin	dieldrin	5.16	0.0044
HE	heptachlor epoxide	5.40	0.01
HCB	hexachlorbenzene	5.45	0.028
PCE	perchlorethene	2.53	0.54
PCB	polychlorinated biphenyls	6.50	0.001 [c]
TCE	trichlorethene	2.33	0.35
MC	methylchloroform	2.47	0.715
TCDD	2,3,7,8-tetrachlordibenzo-*p*-dioxin	6.76 [b]	0.0015

744 a) Travis et al. (1988) if not given otherwise; b) Rippen (1991-2007) if not given otherwise;
745 c) estimate; PCB is a mix of 209 compounds.

Stefan Trapp, Li Ma and Charlotte N. Legind
Figures to Coupled Mother-Child Model for Bioaccumulation of POPs in Nursing Infants

Figure Captions

Figure 1. System overview

Figure 2. Concentrations in nursing mother and child (ng kg^{-1} lipids) after uptake of 25 pg TCDD per day with diet by the mother.

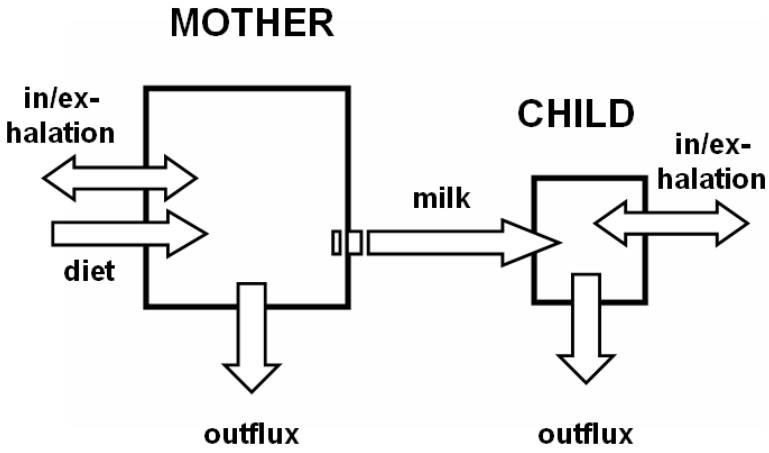
Figure 3. Ratio of the TCDD-dose taken up by the nursing infant (per kg bw) to the dose taken up by the mother (25 pg d^{-1} = 0.42 pg kg^{-1} bw d^{-1}).

Figure 4. Calculated bioaccumulation factor (BAF) mother (t=0) and milk (t=0.5 a) with varying log K_{OW} for low K_{AW} (K_{AW} =10^{-9} L L^{-1}) and high K_{AW} (K_{AW} =0.1 L L^{-1}) compared to the result derived with the regression of Travis et al. (1988).

Figure 5. Calculated ratio of uptake via inhalation to uptake via diet for the assumption of phase equilibrium for mother and child (t=0.5 a) with varying log K_{OW} for high K_{AW} (K_{AW} =0.1 L L^{-1}), moderate K_{AW} (K_{AW} =0.001 L L^{-1}) and low K_{AW} (K_{AW} =10^{-6} L L^{-1}). Dotted line shows ratio 1:1.

Figure 6. Bioaccumulation factors (related to lipid content) for human adipose tissue for 12 neutral organic compounds collected from literature (Lit) compared to the regression by Travis et al. (1988) and the model outcome for mother before birth at steady-state.

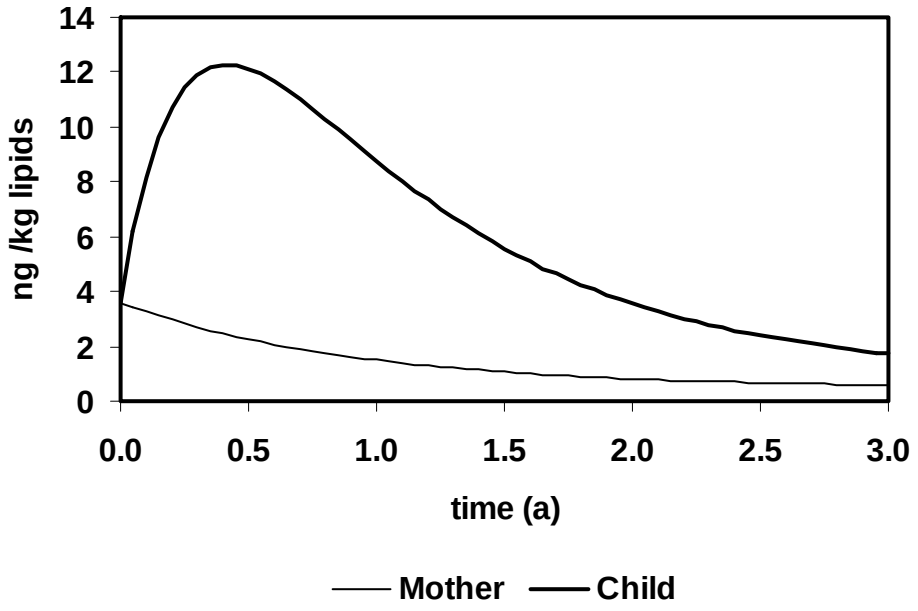
Figure 7. Bioaccumulation factors (related to lipid content) for human milk for 7 neutral organic compounds collected from literature (Lit) compared to the regression by Travis et al. (1988) and the model outcome for t=0 (model t=0, at birth) and t=1 year (model t=1).



781

782 **Figure 1**

783



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785 **Figure 2**

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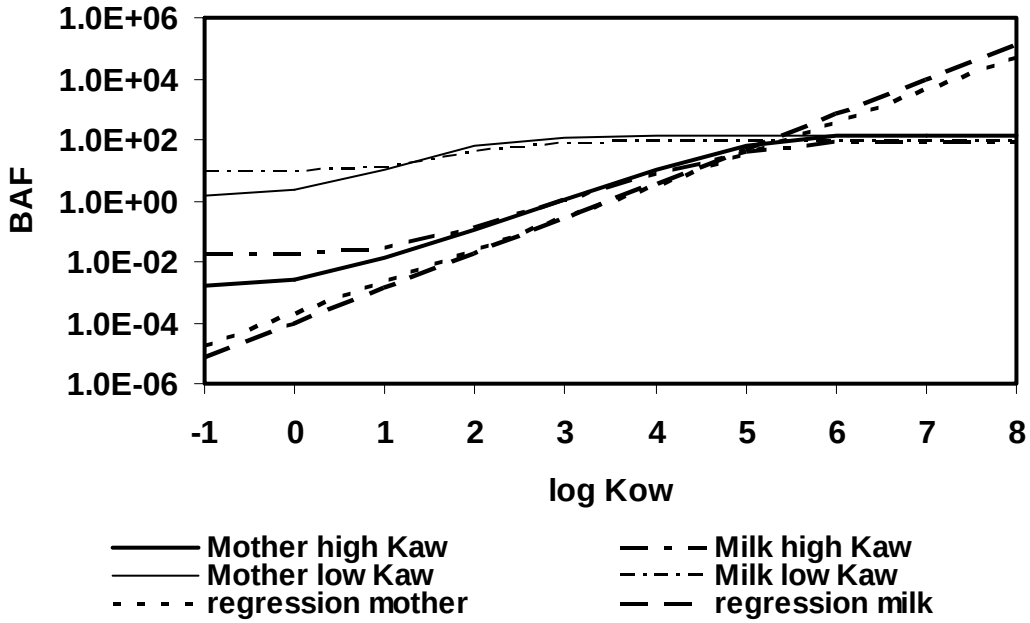
787 **Figure 3**



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789 **Figure 4**

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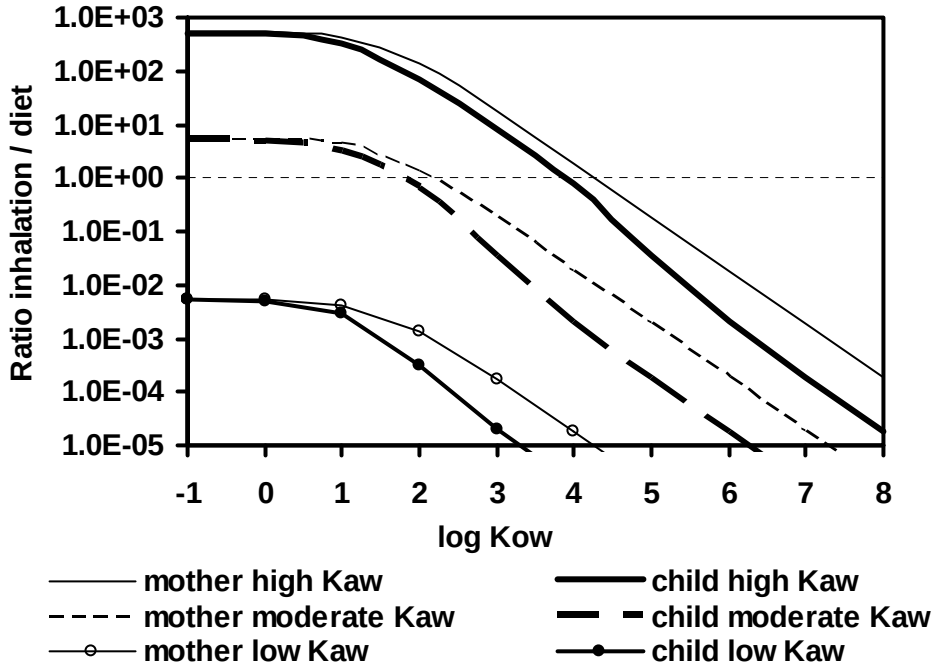

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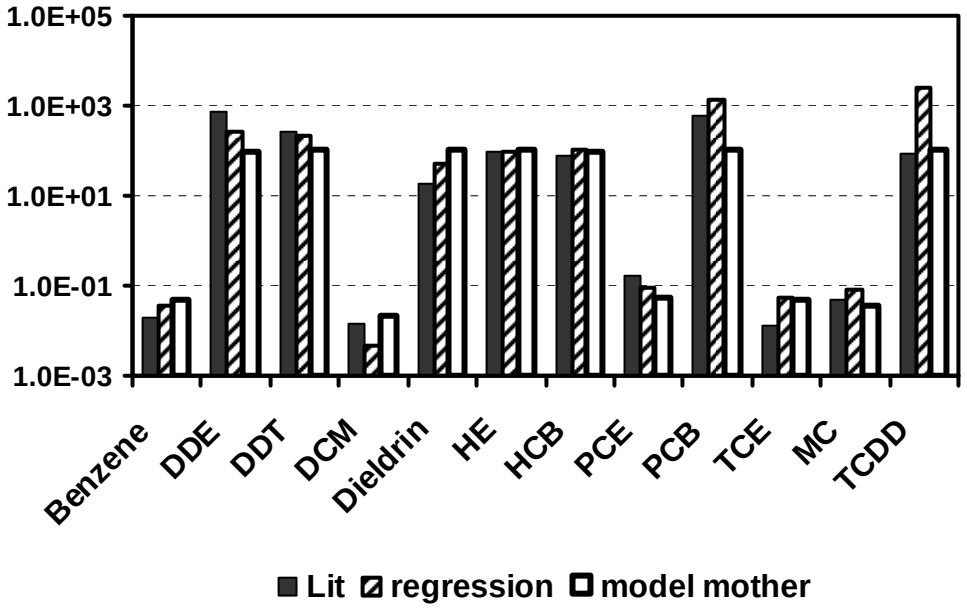
792 **Figure 5**



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794 **Figure 6**

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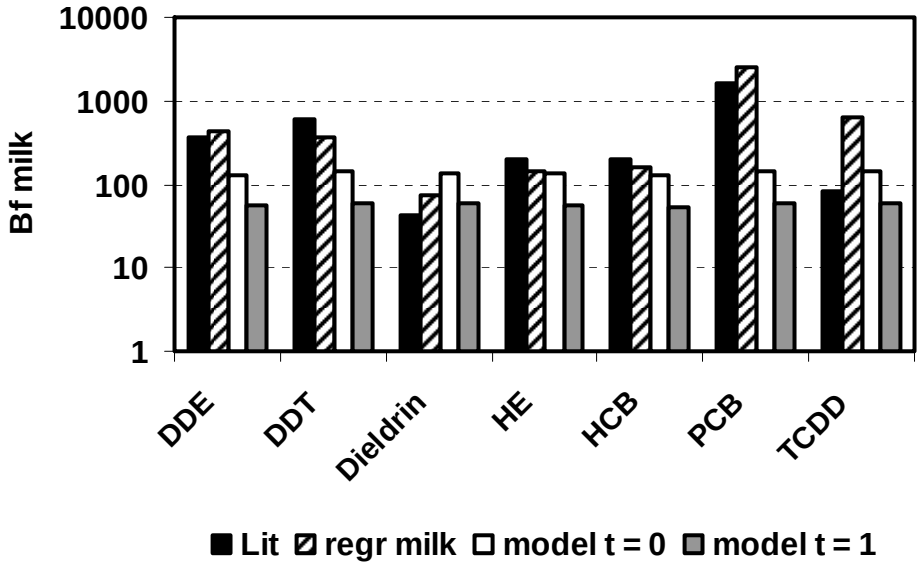

796

797 **Figure 7**

798